APPLICANTS' STATEMENT OF SUBSTANCE OF INTERVIEW

The Applicants wish to thank Examiner Wang and Examiner Saoud for the courtesies extended during the interview that was held on September 2, 2009. The Applicants confirm that the substance of the interview is accurately reflected in the Interview Summary dated September 9, 2009. The potential claim amendments discussed during the interview are reflected in the enclosed amendments. No agreement was reached on allowability of claims.

The Commissioner is hereby authorized to charge any fee which may be required to our Deposit Account No. 02-2095.

REMARKS

The Applicant wishes to direct the Examiner's attention to co-pending applications and patent owned by the assignee: 11/367,609 (Patent No. 7,439,324); 11/565,967; 11/682,217; 11/850,502 and 12/236,731.

By the present amendment, claims 10, 15 and have been cancelled, claims 1, 2, 9, 10, 12, 20, 29, 39, 41, 48, 49 and 51, have been amended and new claims 52-56 have been added. Applicant has amended claims 1, 9, 29, 39, 49 and 51 to replace "blocking agent" with "chemical modifying agent". Support for this amendment is found for example on page 25 which specifies chemical modifying agent as a class of blocking agent and on page 32 lines 19-21. Independent claims 1 and 49 have further been amended to specify that the chemical modifying agent "chemically reacts with and selectively blocks target epitope". Support for this amendment is found for example on page 10 line 20 and page 11 lines 1-2. Claims 1, 2, 20, 39 and 49 have been amended to replace "non-wildtype" with "aggregated or misfolded" (claim 1, 2, 39 and 49) or "aggregated" (claim 20), support for which is found for example on page 11 lines 21-22, page 15 lines 24-30, page 16 lines 1-3 and page 19, lines 22-23. Claims 1, 39 and 49 have been amended to replace "modifying" with "disaggregating or denaturing", claim 12 has been amended to replace "modified" with "disaggregated", support for which is found for example in now cancelled claim 10, on page 10 line 23 and page 20 lines 20-

26, and claims 1, 39, 41 and 49 have further been amended to replace "a detection agent" with "an aptamer or antibody" support for which is found for example in now cancelled claim 15 and on page 20 lines 27-28. Claim 48 has been amended to replace "in a different conformation as compared to the wildtype conformation" with "misfolded", support which is found on page 27 lines 12-15, which specifies a misfolded conformation refers to the folded conformation of polypeptide in a disease or disorder state where the conformation differs from the wild type conformation. New claim 52 specifies target epitopes, support for which is found for example on page 38 in the paragraph describing antibodies; and new claim 53 specifies the chemical modifying agent covalently reacts with the target epitope, support for which is found in the recitation of chemical modifying agents that covalently modify the target epitope such as peroxynitrite, hydrogen peroxide, diethyl pyrocarbonate (DEPC), 4-hydroxynonenal (4HNE), epoxides such as conduritol-B-epoxide and 1,2-epoxy-3-(p-nitrophenoxy)propane, methylene and diazirine. New claims 54 and 55 specify the chaotropic agent is selected from guanidine salts, urea or thiourea, support for which is found for example on the last two lines of page 16. New claim 56 is specific for an embodiment relating to PrP and peroxynitrite, support for which is found for example on page 10 lines 13-30.

Further, claim 30 was inadvertently listed as withdrawn in previous correspondence. The status of claim 30 is presently listed as previously presented.

The amendments to the claims have been made without prejudice. Applicant reserves the right to pursue any of the deleted subject matter in a further divisional, continuation or continuation-in-part application. This Amendment does not contain new matter.

The Office Action dated June 10, 2009 has been carefully considered. It is believed that the claims submitted herewith and the following comments represent a complete response to the Examiner's rejections and place the present application in condition for allowance. Reconsideration is respectfully requested.

Claim Objections:

The Examiner has objected to claim 30 alleging that the status of the claim is not correct. The Applicant thanks the Examiner for directing the Applicant's attention to this inadvertent error. As mentioned above, claim 30 was inadvertently listed as withdrawn in previous correspondence. The status of claim 30 is presently listed as "previously presented".

In light of the above, the Applicant respectfully requests the objection to claim 30 be withdrawn.

35 USC § 112, first paragraph

The Examiner has maintained the objection to claims 1-2, 9-17, 20-22, 29-30, 39, 41, 47-49 and 51 alleging the specification does not reasonably provide enablement for the claimed method of detecting whether a structurally and functionally defined candidate polypeptide with an unknown target epitope is in a wildtype or non-wildtype conformation by using an unknown blocking agent to block an unknown accessible epitope in the polypeptide, modifying and determining whether the modified mutant is a wildtype or non-wildtype conformation as broadly claimed. The Examiner alleges that the Applicant fails to provide sufficient guidance as to enable a skilled artisan to practice the full scope of the claimed invention because the instant specification fails to teach how to make and use all of the structurally and functionally undefined target epitopes, candidate polypeptides, blocking and detection agents in the claimed method.

The Applicant has amended the claims to replace "blocking agent" with "chemical modifying agent", and has further specified in independent claims that the chemical modifying agent "chemically reacts with and selectively blocks target epitope"; has replaced non-wildtype with "aggregated or misfolded" or "aggregated"; has replaced "modifying" with "disaggregating or denaturing"; "detection agent" with "aptamer or antibody"; and has amended claim 49 to replace "in a different conformation as compared to the wildtype conformation" with "misfolded". To the extent that the present

amendments do not address the Examiner's concerns, the Applicant respectfully disagrees and respectfully submits that it is not incumbent upon the Applicant to teach "how to make and use **all**" of the aforementioned elements to enable an invention. The USPTO enablement training materials demonstrate this point in Example C. This Example claims a method (claim 2), which employs a reagent comprising "a substance which inhibits any reaction between fibrinogen and compound X". The hypothetical specification includes a sole example where the "substance" is boric acid. The example describes a scenario where two prior art documents exist, each of which discloses five different compounds which inhibit any reaction between fibrinogen and compound X. All the claims would be enabled because the specification suggests the use of compounds other than boric acid, such other compounds are well known in the prior art as exemplified by the two articles, and the specification need not disclose what is well known in the art, and preferably omits it.

From the present scenario, it is clear that:

1. it is not necessary to disclose **all** of the target epitopes, candidate polypeptides, blocking and detection agents in the claimed method in order to enable the claim

2. **guidance as to any other substances which have the disclosed ability, disclosure of specific characteristics for such substances, guidance as to how or why the "substance" complexes and inhibit the reaction that allows one skilled in the art to predict which substances would react with in a manner similar to working example substance (e.g. boric acid) are all relevant to the enablement inquiry.**

In the present case, the disclosure provides numerous examples of chemical modifying agents, candidate polypeptides that exist in a i) wildtype and ii) an aggregated or misfolded conformation, target epitopes and disaggregating or denaturing agents as well as guidance to other substances (e.g. other antibodies etc) that have the disclosed ability, the specific characteristics of the substances and explanation as to why the substance binds and inhibits the reaction, allowing a person skilled in the art to predict

which substances out of the vast numbers of known substances would be useful in a manner similar to the several working example substances. Examples include:

Chemical modifying agents

The Applicant provides at least the following chemical modifying agents: optionally peroxynitrite, hydrogen peroxide, diethyl pyrocarbonate (DEPC), 4-hydroxynonenal (4HNE) an epoxide such as conduritol-B-epoxide and 1,2-epoxy-3-(p-nitrophenoxy)propane, methylene or diazirine and related compounds [page 16].

Further, working examples are provided for two chemical modifying agents: peroxynitrIte (figures 1-4) and DEPC (figure 5).

Additional guidance on the types of chemical modifying agents is provided on pages 25 and 32. Specifically, the application teaches that peroxynitrite preferentially modifies tyrosine, serine, methionine, histidine and tryptophan as well as cysteine and other amino acids (25, 26). DEPC preferentially modifies histidines (37), and succinic anhydride preferentially modifies residues comprising amines. Epoxides, including conduritol-B-epoxide and 1,2-epoxy-3-(p-nitrophenoxy) propane) are a reactive group used widely for "suicide inhibition" of carboxyl group side chains, such as the catalytic residues of aspartyl proteases (19, 20). Hydrogen peroxide and methylene are also useful. The chemicals may modify the target epitope by oxidizing, nitrating, reducing, or otherwise modifying the epitope.

Further guidance is provided in several examples such as in Example 9 that provides instruction for modifying SOD1 by succinic anhydride and/or DEPC and teaches this property can be exploited to discriminate between aggregated and unaggregated SOD1 protein.

Candidate Polypeptides

Candidate polypeptides are polypeptides that exist in at least two conformations (page 53) and include, as described on page 16, a candidate polypeptide that comprises prion

protein, wherein the wild type folded conformation comprises the conformation of wild type folded prion protein and the misfolded/aggregated conformation comprises the conformation of PrP^{Sc}. Alternatively, the wildtype folded protein comprises the conformation of APP or its cleavage product amyloid beta, and the misfolded conformation comprises the conformation of Alzheimer's disease APP or its cleavage product amyloid beta. In another example, the candidate polypeptide comprises, SOD1, alpha-synuclein, islet amyloid polypeptide, resistin or p53 protein. In addition, the application describes the methods are useful for application to an aggregated polypeptide having a conformation comprising multiple copies of a polypeptide aggregated together through interactions of beta-sheet-rich areas of the polypeptide. In one embodiment, the polypeptide is polypeptide that is aggregated in prion protein aggregates. In another embodiment, the polypeptide is polypeptide that is aggregated in amyloid plaques.

Working examples of PrP (figures 1-3), Abeta (figure 4), SOD1 (figure 5), and alpha-synuclein (figure 6) are provided. Prophetic examples, for example for Tau, are also provided.

Target Epitopes

The application teaches a number of target epitopes (Table on page 38) and how to identify target epitopes (e.g. pages 34-35).

SOD1 target epitopes are provided in Example 9.

Working examples are provided for epitopes in PrP recognized by 3F4 and 6H4; and for epitopes in A-beta recognized by 6E10.

Further optimization of parameters is taught in Example 4.

A number of PrP epitopes (and the antibodies that bind them) are known in the art. Several have further been used successfully in the methods of the invention. For

example, the inventors have demonstrated that target epitopes recognized by antibodies known in the art as POM1 (which recognizes an epitope within amino acids 121-152 of Hu-PrP), 3C8 (which recognizes an epitope within amino acids 214-230 of Hu-PrP), and 5G12 (which recognizes an epitope within amino acids 225-228 of Hu-PrP) are useful in the claimed methods. In addition, antibody 7D9 for which the epitope recognized is not known, is also useful in the methods of the invention.

Denaturing or Disaggregating the Polypeptide

As indicated on page 16, the polypeptide can be denatured disaggregated by a number of agents, for example with heat, detergent and/or chaotropic agents. Examples of chaotropic agents are provided including guanidine salts, urea or thiourea.

Preserving the Candidate Polypeptide in a Wildtype Conformation

The Examiner again alleges that the claimed method is directed to a method of determining whether a protein is in a wildtype or non-wildtype conformation but that the claimed method itself encompasses a step of modifying the polypeptide. Accordingly the Examiner states it is "unpredictable whether all modification methods would preserve the candidate polypeptide in its wildtype conformation". As mentioned, the Applicant has amended the claim to replace "non-wildtype conformation" with "aggregated or misfolded conformation" and has replaced "modifying" with "disaggregating or denaturing". The Applicant respectfully, further submits that it is not necessary for the candidate polypeptide to maintain its wildtype conformation during the method steps claimed. The conformation state of the polypeptide in the sample before any of the steps is the conformation of interest for obtaining diagnostic information. Accordingly, it is not necessary to maintain the polypeptide in its original conformation throughout the steps of the assay.

Relationship Between the Prion PrP and Other Known Polypeptides

The Examiner alleges that the specification fails to teach the structural and functional relationship between the prion PrP and other unknown polypeptides. The Applicant respectfully submits that the structural relationship between PrP and other polypeptides is conformation. The polypeptides are all related structurally in that they exist in a wildtype folded conformation and also exist in an aggregated or misfolded conformation. For example, the Applicant states on page 9:

> In prion diseases, the normal cellular monomeric prion polypeptide PrP^{C} undergoes refolding to an abnormal, aggregated isoform, generically designated PrP^{Sc}. Diseases such as AD, PD, LBD, ALS and HD are also characterized by misfolded and/or aggregated conformations of cellular proteins. This property is exploited by the methods of the invention to provide sensitive and specific diagnostic tests for these and other diseases.

Clearly the relationship is addressed.

Similarly, the relationship between peroxynitrite and other chemical modifying agents is disclosed. The chemical modifying agents bind or react with an epitope or amino acid as mentioned above comprised in an epitope such that a detection agent cannot recognize the epitope. In aggregated or misfolded conformations, the epitope that is blocked is hidden from the chemical modifying agent. When the aggregated polypeptide is disaggregated, epitopes that were not chemically modified because they were inside the aggregated polypeptide, become exposed and detectable.

In light of the above, the Applicant respectfully submits that the specification clearly discloses a number of methods for using the claimed invention that correlate to the entire scope of the claims and respectfully requests that the objections to the claims under 35 USC §112 first paragraph for lack of enablement be withdrawn.

35 USC §112 first paragraph

The Examiner has rejected claims 1-2, 9-17, 20-22, 29-30, 39, 41, 47-49 and 51 as failing to comply with the written description requirement. For the reasons stated above,

the applicant respectfully disagrees. As mentioned the specification provides numerous examples and teaches a number of candidate polypeptides, chemical modifying agents, denaturing and disaggregation steps and agents and aptamers or antibodies for use in the methods as previously described.

The Examiner disagrees and suggests that the specification only describes detecting epitopes recognized by antibodies 3F4 and 6H4 in acid and peroxynitrite treated brain homogenate in the presence of guanidine as compared to mock treated brain homogenate. Assessing whether the written description requirement is met should include a full review of the application. The review includes comparing the claim scope with the scope of the description and not merely the exemplary support. Further the Applicant respectfully submits that a person skilled in the art would readily recognize that the applicant was in possession of the claimed invention as a whole at the time of filing as there is actual reduction to practice. Further a representative number of species for each claim element is provided. Also, the level of skill in the art is high. As indicated in Example 16 of the Written Description training materials, a working example showing use of a specific nucleic acid species is considered sufficient to satisfy the written description requirement for nucleic acids as a species. The sequence of the nucleic acids was not required to satisfy the written description requirement in the example.

The Examiner alleges that specification fails to teach what other polypeptides (e.g. other than PrP) can be detected by the claimed method in a specific manner. As the chemical modifying agents claimed chemically react with amino acids, the constituents of polypeptides, any polypeptide that can exist in at least two conformations is contemplated. Further, as specified above, working examples of detection of conformations of Abeta, SOD1 and alpha-synuclein are also provided as well as prophetic examples for other polypeptides such as Tau. Accordingly, the Applicant respectfully submits as all polypeptides comprise amino acids that can react with the claimed chemical modifying agents and as working examples of several other proteins are provided, that the specification does indeed teach what other polypeptides can be detected by the claimed method in a specific manner.

The Examiner adds: "there is no specific structural or functional relationships between PrP and other proteins than can be detected by the claimed method. There is no information about any particular portion of the structure that must be conserved for the claimed genus of structurally and functionally undefined candidate polypeptides...". As argued above, the structural/functional relationship between PrP and other proteins is the property of existing in two conformations, wildtype and aggregated or misfolded, where an epitope is accessible in one conformation and inaccessible in the other. The epitope is by definition a sequence of contigous or non-contiguous amino acids, which is recognized and bound by for example an antibody. The epitopes recognized by antibodies is in many cases known. Epitopes are related in that they consist of amino acid residues that can be altered by a chemical modifying agent such that the known antibody that binds the particular epitope no longer binds and detects the polypeptide when the chemical modifying agent is present. Contrary to the Examiner's suggestion, a particular portion of the structure must not be conserved. The 3D structure of the polypeptides and epitopes must provide for the target epitopes to be exposed in one conformation and available to chemical modification and hidden in another conformation and consequently unavailable to chemical modification. The Applicant respectfully submits that the relationship is sufficient such that a person skilled in the art would readily know or be able to determine using routine methods (e.g. such as non-denaturing western blotting techniques) if the candidate polypeptide exists in two conformations. Accordingly, the Applicant respectfully submits, that the written description requirement is met by the present specification.

In light of the above, the Applicant respectfully requests that the rejection to the claims for failing the written description requirement, be withdrawn.

Double patenting

The Examiner has objected to claim 49 alleging it is a substantial duplicate of claim 1 The Applicant respectfully disagrees. In claim 1, the target epitope is initially inaccessible in the aggregated or misfolded conformation and initially accessible in the

wildtype conformation whereas in claim 49, the target epitope is initially inaccessible in the wild-type conformation and initially accessible in the aggregated or misfolded conformation. Accordingly, the Applicant respectfully submits that the subject matter is not overlapping as a polypeptide that meets the elements of claim 1 will not meet the elements of claim 49 and vice versa.

The Examiner has rejected claims 1, 2, 12 15-17, 20-22, 29-30, 39, 41, 47-49 and 51 on the ground of non-statutory obviousness type double patenting over claims 18-22 of US Patent No 7041807 (Cashman '807). The Examiner suggests that the claims of Cashman '807 "are directed to a method for detecting PrPSc in a biological sample using an antibody that is able to recognize PrPSc wherein the antibody selectively binds to PrPSc". From this statement the Examiner concludes that the '807 patent is a species that anticipates the generic claimed method "because the claimed method is directed to a method of detecting all forms of polypeptides including PrPSc using all forms of detecting agents including antibodies against PrPSc. In addition since the instant claims do not limit the blocking agent used in the claimed method, any agent including the antibody in '807 meets the limitation of blocking agent and thus anticipates the claims".

The Applicant has amended the claims to replace "blocking agent" with "chemical modifying agent" that chemically reacts with selectively blocks accessible target epitope. The claims in Cashman '807 do not react a chemical modifying agent with target epitope. Accordingly, the Applicant respectfully submits that the claims in Cashman '807 are patently distinct.

In light of the above the Applicant respectfully requests that all the double patenting rejections be withdrawn.

35 USC § 102

The Examiner has maintained the rejection to claims 1-2, 9-17, 20-22, 29-30, 39, 41, 47-49 and 51 as being anticipated by US2002/0123072 (Prusiner) and US 6677125 (Prusiner). Specifically the Examiner alleges "Prusiner teaches a method of detecting

the presence of a disease related to conformation of a protein PrPSc (non-wildtype conformation) and a non-disease related conformation of the protein (PrPc (wildtype conformation) in a sample using an antibody specific for PrPSc", which the Examiner alleges meets the limitations as recited in the objected to claims.

As mentioned, the Applicant has amended the claims to replace "blocking agent" with "chemical modifying agent that chemically reacts with the target epitope". The Prusiner application and patent do not disclose reacting a chemical modifying agent with target epitope. Accordingly, the Applicant respectfully submits that Prusiner does not anticipate the objected to claims.

To the extent the above does not address the Examiner's concerns, the Applicant respectfully disagrees and submits that the above recitation does not meet the limitations as recited in the objected-to claims. The Examiner does not identify any or all of the instant claim elements in Prusiner and therefore cannot conclude that method taught by Prusiner "meets the limitations as recited in the objected to claims". In fact, the Applicant respectfully submits, that none of the various assays taught in Prusiner US'072 is embraced by the present claims. The Examiner only alleges that Prusiner's assay does teach the step of contacting the polypeptide with a blocking agent as Prusiner teaches pretreatment of samples with antibodies binding to the non-disease conformation of the protein. As blocking agent has been replaced with "chemical modifying agent" that chemically reacts with target epitope, the Examiner's objection is moot

The Examiner has maintained the rejection of claims 1-2, 9-17, 20-22, 29-30, 39, 41, 47-49 and 51 as being anticipated by US 7041807 (Cashman). The Examiner alleges that Cashman teaches a method for detecting PrPSc in a biological sample using an antibody that is able to recognize PrPSc wherein the antibody selectively binds to PrPSc as set forth in section ODP.

As mentioned above, the claims have been amended to claim a "chemical modifying agent" that chemically reacts with target epitope. Further, practicing the method according to Cashman '807 would not result in determining whether the polypeptide was in a 1) wildtype or 2) aggregated or misfolded conformation. Accordingly, the Applicant respectfully submits that Cashman '807 cannot anticipate the objected to claims.

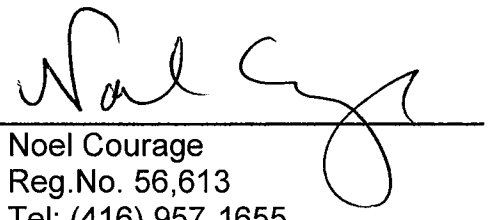
In light of the above, the Applicant respectfully requests that the objections to the claims under 35 USC §102 be withdrawn.

In view of the foregoing, we respectfully submit that the application is in order for allowance and early indication of that effect is respectfully requested. Should the Examiner deem it beneficial to discuss the application in greater detail, he/she is kindly requested to contact Noel Courage at his convenience.

The Commissioner is hereby authorized to charge any deficiency in fees or credit any overpayment to our Deposit Account No. 02-2095

Respectfully submitted,

Bereskin & Parr LLP/S.E.N.C.R.L., s.r.l

By 

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